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Uterine Artery Embolization:

A Systematic Review of the Literature and Proposal for Research

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Health

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OVERVIEW

Objectives:

Uterine leiomyomata are a common cause of gynecologic symptoms and major gynecologic surgery. Common treatments for these benign tumors include medical therapy, hysterectomy, and myomectomy. The objective of this project was to review and synthesize the existing literature on a minimally invasive technique for reducing symptoms from uterine leiomyomata, uterine artery embolization (UAE); and, using an expert panel approach, develop an agenda for research into the long and short term outcomes of this technique.

Literature Search Strategy

We conducted a literature review of Medline (1990-May 1999) using the terms: uterine fibroid embolization, uterine artery embolization, leiomyomata and embolization, fibroids and embolization, and embolization and uterus. Literature was also identified by requesting reference lists from authors of papers identified via Medline and expert panel members, and by reviewing reference lists from identified articles. Authors of papers were asked about ongoing trials and unpublished reports. Abstracts were also identified from a comprehensive hand search of the SCVIR Annual Scientific Meeting Program 1996-1999, and from a targeted search of programs from other relevant scientific meetings.

Selection Criteria

All titles, abstracts of non-rejected articles, and full text of the remaining articles were reviewed. Several European reports were translated into English and reviewed. Inclusion criteria were: human studies of vascular embolization to control symptoms of uterine leiomyomata presenting numerical data. Case reports, review articles, letters, and editorials were excluded.

Data Collection and Analysis

Data from articles and abstracts meeting the criteria were abstracted into evidence tables. Weighted averages of key measures were calculated. All articles and abstracts selected consisted of case series without control groups.

Comparative Data

Data on the two most common invasive treatments for uterine leiomyomata—hysterectomy and myomectomy—were collected from the literature and summarized into evidence tables comparing these procedures to the reported UAE results collected from the literature review.

Expert Panel

A ten member expert panel, chosen to provide breadth of knowledge and represent diverse interests, examined the literature review. Using a modified Delphi process, the panelists rated a comprehensive list of outcomes with regard to their importance for research into uterine artery embolization. The panel then agreed on four areas and/or specific studies they felt needed to be conducted in order to adequately evaluate the utility of UAE.

CLINICAL BACKGROUND

Uterine Leiomyomata: Definition and Symptoms

Uterine leiomyomata (sometimes called uterine fibroids) are benign tumors resulting from the neoplastic transformation of a single smooth muscle cell (Townsend, 1970). Myomata may arise throughout the body (e.g., from smooth muscle cells in arterioles found in lung or other organs), but most commonly present in the uterus, ranging in size from several millimeters to more than 20 centimeters. Although the mechanisms controlling leiomyoma growth are not fully understood, their growth does appear to be regulated by steroid hormones (estrogen and progesterone), peptide growth factors (such as epidermal growth factor), and the availability of adequate vascular perfusion (Buttram, 1981).

Uterine myomata are generally asymptomatic, with studies estimating that between 60 and 90% of such tumors fail to cause any symptoms (ACOG, 1994). Those that do

produce symptoms typically do so during the late reproductive years to the perimenopausal period. Size and location may play a role in determining which myomata will become symptomatic, but these two factors alone do not explain the variation in symptomatology seen in clinical practice.

Leiomyomata are generally diagnosed on physical examination, by finding either an enlarged or irregularly shaped uterus in the absence of other abnormalities (e.g., ovarian masses) suggesting another diagnosis. Diagnosis may be supported by radiologic studies (typically ultrasound), hysteroscopy, or laparoscopy.

Abnormal menstrual bleeding is the most common symptom causing women with uterine fibroids to seek medical care, although both leiomyomata and menstrual disorders (in the absence of myomata) are so common in the general reproductive age population that some of the association between bleeding problems and leiomyomata is probably coincidental. The exact mechanism by which fibroids cause increased menstrual blood loss is not known, although several theories have been advanced. Myomata located within the walls of the uterus (intramural myomata) may compress uterine veins as they grow, leading to venular ectasia and perhaps impairment of normal hemostatic mechanisms. Submucosal myomata (those protruding into the endometrial cavity) have been postulated to cause increased bleeding as a result of ulcerations developing over the tumor. Finally, uterine myomata may dramatically increase the surface area of the endometrium, thereby increasing the area from which menstrual blood loss may be expected (Buttram, 1981).

Leiomyoma may also cause pelvic pain, either through a mass effect, or by the spontaneous necrosis of the tumor. Acute onset pelvic pain may occur when a myoma either outgrows its blood supply, producing a necrotic central core, or when a pedunculated fibroid undergoes torsion on its stalk and becomes ischemic. Pelvic discomfort, pressure, or pain may also result from compression of adjacent organs by an enlarging fibroid uterus. Urinary frequency and constipation may result from compression of bladder or bowel, respectively.

The link between uterine leiomyomata and infertility, while frequently discussed, has not been convincingly established. In certain cases, such as when blockage of the cervix or

fallopian tubes by myomata is demonstrated, the tumors certainly may impede normal fertility. In other cases, when myomata distort the uterus and infertility is present, the association may be purely coincidental. There are multiple case series demonstrating improved individual fertility after myomectomy (that is, a previously sub-fertile couple conceiving after myomectomy), but there are no data comparing myomectomy to other treatments (such as watchful waiting, or medical therapy) with regard to pregnancy rates or outcomes (Buttram, 1981).

Uterine leiomyosarcoma is a rare tumor with a poor prognosis that does not appear to be related to uterine leiomyomata. That is, women with leiomyomata are not at increased risk for sarcoma. However, because of its rarity and lack of clear symptoms, leiomyosarcoma is often discovered at the time of surgery for what are believed to be leiomyomata. This occurs in approximately 0.1 – 0.3% of such surgeries in reproductive age women, and in as high as 1% of such procedures in postmenopausal women (ACOG, 1994).

TREATMENT

Medical Treatment

When clinically diagnosed, uterine myomata are frequently asymptomatic and rarely represent malignancy, therefore treatments are reserved for symptomatic patients. Primary therapy for bleeding (which accounts for the bulk of symptoms) is medical, and includes the use of hormonal agents such as progestins, combined oral contraceptives, and (less commonly, and for short term treatment) gonadotrophin release hormone analogues (GnRHa's). Non-hormonal treatments include non-steroidal anti-inflammatory agents (NSAID's), and in the U.K., though not in the U.S. where they lack FDA approval, anti-fibrinolytics agents. Progestin releasing intra-uterine devices (IUD's) are used in the U.K. and other countries to treat menorrhagia, but in the U.S. their use remains rare.

Surgical Treatment

Medical therapy may fail to control symptoms in up to two-thirds of patients with bleeding and a higher proportion of those with mass related symptoms. Those women who fail or refuse medical therapy are candidates for more invasive treatments, such as hysterectomy or myomectomy. Hysterectomy remains the predominant invasive treatment for uterine fibroids in the U.S., with between 177,000 and 366,000

hysterectomies performed each year for this problem (National Center for Health Statistics, 1998; Lepine, 1997). Hysterectomy is a relatively safe procedure, with a major complication rate of 1-2% and a death rate of 0.1%, and guarantees permanent relief from symptoms of myomata (Bernstein, 1996). It is, however, a major abdominal surgery with a substantial recovery period. Hysterectomy also removes an organ which may play a role in sexual function, guarantees infertility, and has important psychological implications for many women.

Myomectomy, or surgical removal of the leiomyoma without removal of the uterus, may provide relief from symptoms without some of these drawbacks. In particular, since the uterus is conserved, future childbearing may be possible; sexual and psychological implications of hysterectomy may also be avoided. Estimates of the total number of myomectomies performed in the U.S. are difficult to make, as these procedures are often not coded as being performed for uterine fibroids, but at least 35-40,000 transabdominal myomectomies are done in U.S. hospitals each year (National Center for Health Statistics, 1998).

Burden of Disease

We found no adequate estimates of the burden of disease from uterine myomata in the literature. Recent studies have shown that most patients having hysterectomy for fibroids have significant impairment in their ability to perform their usual activities, often taking 2 or more days per month off work or usual activities. These women often have symptoms for at least 6 months before surgery (Rowe, 1999). Estimating the number of days lost based only on those women having hysterectomy for myomata (177,000-366,000 per year) yields between 2-4 million person-days per year lost to work or other activities before surgery, and an additional 3-7 million person-days after surgery.

It is difficult, given the limited information on uterine myomata, to compare directly the burden of disease from this condition to others. One estimate can be made based solely on the annual number of days women are hospitalized due to leiomyomata. Hysterectomy results in over 900,000 hospital days per year (based on midpoint of estimated number of hysterectomies performed for uterine myomata, 1:4 ratio of vaginal to abdominal hysterectomy, 2 day stay for vaginal and 4 days for abdominal hysterectomy). Using this conservative estimate, leiomyomata would be responsible for

more hospital days than AIDS, breast cancer, dementia, cirrhosis, prostate cancer, or epilepsy (Gross, 1999).

Calculations based on the number of surgical procedures done to treat this condition can provide a lower bound estimate of direct cost to health care payers.

- 600,000 hysterectomies done every year in the U.S.
- 177,000-366,000 are done for symptoms of uterine myomata
- Hysterectomy costs approximately $6,000
- $1 to 2 billion/year direct costs for hysterectomy

For myomectomy:

- 37,000-44,000 myomectomies done each year in the US
- Myomectomy costs approximately $5000
- $2 hundred million/year in direct costs for myomectomy

Thus, the minimum estimated direct cost of treating uterine myomata is over $1 billion per year (in 1999 dollars), with some estimates of direct cost as high as $3 billion per year (Greenberg, 1995).

Uterine Artery Embolization

Uterine artery embolization (UAE) is an emerging minimally invasive technology for reducing symptoms from uterine fibroids. It has been proposed as a less invasive alternative to current treatment for these common, benign uterine tumors. As previously noted, U.S. gynecologists perform more than 150,000 hysterectomies and 35,000 myomectomies each year to relieve symptoms of uterine fibroids. Thus, if research demonstrates its safety and efficacy, UAE has the potential to benefit hundreds of thousands of patients each year. Despite this large potential benefit, the current body of research on UAE is quite limited, with fewer than 500 procedures reported in the literature, and no trials prospectively comparing UAE to more conventional procedures. In order to better understand the current evidence surrounding uterine artery embolization, we performed a systematic review of the literature, summarized the outcomes from the procedure, and compared them to the more common treatments for leiomyomata.

Uterine artery embolization has been performed using either general anesthesia or conscious sedation. Some practitioners administer prophylactic antibiotics, usually a cephalosporin. An angiography catheter of variable size (generally 4 or 5 French) is inserted directly into the patient's femoral artery, and a single uterine artery is then selectively catheterized. Radioopaque die is injected, and the vessels examined under fluoroscopy. Embolic material (generally polyvinyl alcohol particles between 150-700μm in size) is released until the uterine vessel is occluded. The catheter is then either withdrawn entirely and the process repeated beginning with puncture of the contralateral femoral artery, or the catheter is withdrawn to the level of femoral artery, passed through the distal aorta, and maneuvered to the contralateral uterine artery without repuncture. Occlusion of the uterine vessels is confirmed by angiography and the catheter is removed. The procedure takes between 45-135 minutes to complete and the patient is exposed to approximately 20 rads (20 cGy) of ionizing radiation to the ovaries (compared to 2-3 rads during a CT scan of the pelvis, although this exposure may fall with continued experience with UAE). (Goodwin, S; personal communication). Patients are observed for up to 24 hours post-procedure, with some practitioners admitting patients to hospitals and others observing them in outpatient units.

SYSTEMATIC LITERATURE REVIEW

Expert Panel

A ten member expert panel was convened at RAND to examine the literature review on UAE and develop a consensus for future research in the field. Panel members were chosen to provide breadth of knowledge and represented diverse interests. Panelists were identified through medical specialty societies, literature, and expert opinion, and their participation solicited. They included interventional and non-interventional radiologists, obstetrician-gynecologists, a medical ethicist, experts on technology assessment and health policy, and a consumer advocate. Economists, health services researchers, and a statistician also attended the meeting. Expert panel members are listed in Appendix A and other conference participants in Appendix B.

Literature Search Strategy

Trained health services researchers performed a literature review of Medline (1966-May 1999) using the terms uterine fibroid embolization, uterine artery embolization,

leiomyomata and embolization, fibroids and embolization, and embolization and uterus. Literature was also identified by requesting reference lists from interventional radiologists known to perform the procedure (identified by membership in the professional society of interventional radiologists), authors of papers identified via Medline, and expert panel members. Abstracts were also identified from a comprehensive hand search of the SCVIR Annual Scientific Meeting Program 1996-1999, and from a targeted search of programs from other relevant scientific meetings. References of identified articles were also searched for previously unidentified reports. Authors of papers on UAE were asked about ongoing trials of the procedure (conducted by them or other investigators) and unpublished reports. Authors of multiple reports were contacted and asked to identify any papers or abstracts which presented data on patients who had been the subject of previous reports. Duplicative reports were excluded from analysis.

Selection Criteria

After all titles were reviewed, abstracts of non-rejected articles were reviewed. Full length articles were reviewed for all papers identified, except those presented only as abstracts. Abstracts presented at conferences were reviewed in full. Several reports in the European literature were translated into English and reviewed. Articles were selected for inclusion if they were human studies of embolization of the uterine/pelvic vasculature to control symptoms of uterine leiomyomata and reported numerical data on at least one outcome measure. Case reports, review articles, letters, and editorials were excluded.

Data Collection and Analysis: UAE Literature

Articles presenting data on the outcomes of UAE for uterine leiomyomata were evaluated by two trained researchers for their relevance. Published abstracts were similarly reviewed. Data from articles were abstracted into evidence tables. All articles and abstracts selected consisted of case series without control groups (USPSTF Level III), (USPSTF, 1996). As all data were derived from case reports, simple weighted averages were calculated for measures with adequate homogeneity. If measures differed significantly among reports, ranges, rather than point estimates, were reported. The evidence table was reviewed by the expert panel and comments solicited.

Comparative Data—Hysterectomy and Myomectomy

Data on the two most common invasive treatments for uterine leiomyomata—hysterectomy and myomectomy—were summarized into evidence tables. Data on hysterectomy were derived from a comprehensive review of the literature on hysterectomy published in 1996, as well as from a systematic review of evidence published since 1996. Data on myomectomy were obtained using a search strategy similar to the one outlined above, substituting uterine leiomyomata, myomectomy, outcomes, and complications as the search terms.

Main Results of Literature Review

Treatment Methods:

Hysterectomy is the most common invasive treatment for uterine myomata, with 5-10 times as many hysterectomies for fibroids being performed as myomectomies, and these numbers have remained relatively stable over the last decade (Table 1). Currently, uterine artery embolization accounts for a negligible proportion of invasive treatments for myomata (800 procedures estimated in 1998) and is generally performed on a slightly older population than the other treatments (Table 2).

Outcomes:

Comparative results of hysterectomy, myomectomy, and uterine artery embolization demonstrate similar outcomes for all three procedures, with a significant number of patients experiencing at least short term relief from symptoms (Table 3). No adequate data exist for longer term outcomes of UAE, such as recurrence of myomata, premature menopause, or improvement on quality-of-life indices. Complication rates also appear similar, with one reported death in 1,500 UAE procedures (Vashisht, 1999) and a death rate from hysterectomy of 11 per 10,000 cases (Bernstein, 1997). The short term rate of re-operation (i.e. hysterectomy following UAE or myomectomy, or surgery to repair intestinal injury after hysterectomy) appears higher after UAE (approximately 5% for UAE and 1% or less for hysterectomy and myomectomy) (Bernstein, 1997; Iverson, 1996). Rates of post-operative wound infection, fever, and thromboembolic events do not appear to differ significantly, based on the limited available data.

Data Quality:

Comparison across these procedures is severely hampered by the near absence of comparative data in the literature. Only one comparative study of hysterectomy and myomectomy was identified (USPTF Level II), and all published studies of UAE are uncontrolled case series (USPTF Level III). As a result, unmeasured differences in patient characteristics could significantly impact these comparisons. Furthermore, the data presented in the evidence tables has not been corrected for age, severity of illness, or any other potential confounders. For these reasons, we elected not to calculate confidence limits around these numbers, or make statistical comparisons. We instead present the data in Table 3 as a way to allow qualitative comparisons among procedures.

Panel Process

We convened a ten member expert panel at RAND to examine the results of the literature review and suggest directions for research. Before the meeting, panelists were provided with background on uterine myomata, UAE, hysterectomy, and myomectomy, the evidence table (Table 3), a literature summary (Table 4), and the original articles used to create the evidence tables. Panelists were presented with a list, developed by RAND staff, of 41 outcomes which potentially could be measured in studies of treatments for leiomyomata. At the meeting, panelists used a modified Delphi process, to independently and anonymously rate the importance of measuring each of these outcomes. Each outcome most highly rated by the group was discussed and several new ones added. Participants then rated the outcomes independently a second time. The panel then discussed the feasibility and importance of collecting key outcome measures using a variety of experimental designs. During the meeting, panelists were given brief presentations on uterine leiomyomata, UAE, and on various study methodologies.

Outcome Ratings

Panelists agreed that to be accepted by clinicians, studies of UAE would have to examine certain key measures. In the final round of ratings, all ten panelists identified the following short term (defined as occurring less than 45 days after the procedure)

outcomes as either "important to measure" or "essential to measure" in studies comparing UAE to other invasive treatment modalities:

- death
- reoperation (e.g. hysterectomy for infection following UAE)
- operative injury.

All ten panelists similarly identified the following key long term (occurring greater than or equal to 45 days after the procedure) outcomes as being "important" or "essential" to measure:

- menorrhagia
- premature menopause
- recurrence of myomata requiring hysterectomy or myomectomy
- mental health (e.g. as measured by the Mental Health Index from the SF-36)
- pain during sexual activity
- satisfaction with treatment
- technical failure rate of the procedure (e.g. inability to successfully cannulate uterine artery)
- frequency of use of medical therapy after the procedure (e.g. hormonal therapy to control bleeding)
- quality of life (as measured by a disease-specific quality-of-life instrument).

A majority of the panelists rated the following outcomes as "essential" and no panelists felt they "should not be measured":

- transfusion
- operative site infection
- pelvic pain
- anemia
- enjoyment of sexual activity
- frequency of sexual activity
- direct and indirect costs of treatment
- length of hospital stay
- number of follow-up visits until full recovery

The final outcome ratings for the entire panel are given in Table 5.

RESEARCH AGENDA

The literature review, evidence tables, and outcome ratings were used by the panelists as a basis for a thorough discussion of the direction future research into uterine artery embolization should take. The majority of panelists agreed that, while the case series reviewed for this report were encouraging, they cannot be used as the sole basis to support the general use of UAE in place of more standard treatments; and that unless there was high quality data comparing it favorably to more widely practiced invasive treatments (i.e., hysterectomy and myomectomy), UAE would not become a generally accepted treatment.

There was consensus that research must be undertaken to address questions about the efficacy (including changes in quality of life), risks, and cost of UAE as compared to myomectomy and hysterectomy. It was felt that this research should include, but not be limited to randomized trials comparing UAE to alternative treatments. Based on the panel discussion and the outcome ratings, a series of research questions emerged. For several of these questions, the panel agreed on specific measures or types of measures which should be used to answer the key research questions. The research questions and measures agreed upon are given below.

RESEARCH QUESTION	MEASURES
1. What is the comparative efficacy of UAE, myomectomy, and hysterectomy to control menorrhagia and pain from, and prevent recurrence of, uterine leiomyomata?	Use of medical treatment for fibroids after surgery
2. How is quality of life, affected by each of these treatments?	Disease specific QOL instrument
3. What is the relative level of improvement in mental health, provided by each of these treatments?	Mental Health Index, SF-36
4. What is the comparative satisfaction level of women having each of these three procedures?	No measure identified
5. What is the relative frequency of short term complications (i.e., death, operative	For premature menopause: FSH level

	injury, and reoperation) and long term complications (e.g., premature menopause) from these procedures?	
6.	What are the relative resource costs (as distinct from charges) of each of these procedures?	No measure identified
7.	How do patient and disease characteristics predict the technical success rate of UAE?	No measure identified

Using a nominal group process, the panelists were individually invited to describe what they felt would be the single best study (without consideration of cost) to examine the questions described above. After all panelists had the opportunity to describe a study or area of research, all panelists were invited to ask questions and discuss the strengths and weakness of the various approaches. Eight distinct ideas were put forth and discussed. Consensus developed around the four research elements which the panelists felt would be most likely to advance the body of research on UAE, while satisfying both clinicians and those who make health plan coverage decisions. These proposals were:

- a randomized trial of UAE compared to surgical treatment for myomata
- development of a prospective registry of patients being treated with UAE
- development of a disease specific quality of life measure for women with uterine myomata
- comparative cost analysis of UAE compared to myomectomy and/or hysterectomy

The nature of these proposals is such that they may be carried out, not as separate studies, but rather as interlocking components of a broader research agenda. Specifically, a registry of patients undergoing UAE could be started immediately (indeed, SCVIR is already developing a simple UAE registry, [Landow, W. personal communication]. This registry could provide the basis for identification of sites willing to participate in a randomized trial. A disease specific quality-of-life instrument for symptomatic myomata could be used as one measure of outcomes in a randomized trial. Finally, data on cost could be obtained both in studies designed to specifically examine cost, as well as by examining measures of cost and use of services collected as part of an RCT.

Randomized Trial of UAE

Seven panelists initially proposed randomized controlled trials to evaluate UAE in comparison to various other treatments for uterine myomata, and all panelists agreed that without an RCT, embolization would be unlikely to be widely accepted by gynecologists as an effective treatment for symptomatic myomata. Several areas of concern arose during discussions of possible RCT's. Some panelists were concerned that an RCT might not enroll an adequate number of patients; based on the belief that women would be reluctant to enroll in a trial randomizing them to embolization versus hysterectomy. Expert panel members also debated the proper comparison group for a randomized trial, with some suggesting hysterectomy, some myomectomy, one medical therapy, and some more than one comparison group. There was further concern about carrying out a three-armed RCT comparing hysterectomy, myomectomy, and UAE; both because of the number of patients needed, and because of concerns that neither gynecologists nor their patients would allow the choice between myomectomy and hysterectomy to be made at random.

After a discussion of these concerns, the group agreed that a hybrid trial, involving randomization between surgical therapy (hysterectomy or myomectomy) and UAE, would satisfy these concerns. Such a trial could be conducted as a cohort study nested within an RCT as follows: patients would be randomly assigned to surgery or UAE. The patient and her gynecologist would then make the choice between hysterectomy and myomectomy, based on clinical factors or patient preference. A patient assigned to UAE whose symptoms were not relieved would be offered the choice of repeat embolization or surgery (with the specific procedure chosen by the patient and gynecologist). Myomectomy failures (i.e., persistent significant symptoms) would be offered any of the three available treatments (hysterectomy, repeat myomectomy, or embolization).

This design, shown in Figure 2, has both advantages and disadvantages. Key advantages of RCT's in general include elimination of bias in patient selection, good internal validity, and high face validity among clinicians. Disadvantages include high cost, long delay in obtaining results, and less external validity (as patients and procedures are typically more carefully selected and carried out during an RCT than in usual clinical practice). In addition, recruiting patients into randomized trials of surgical

procedures may be more difficult than recruiting for studies of other types of interventions.

A hybrid design such as the one being proposed addresses some of the disadvantages of RCT's but creates additional concerns. Because an element of patient choice has been maintained, patient recruitment may be easier and therefore the cost may be less. Fewer patients are needed to compare surgery to UAE in this trial than would be needed in a three-armed study of UAE vs. myomectomy vs. hysterectomy. Finally, the nested cohort design allows investigators to collect additional (non-experimentally derived) data concurrently with the randomized portion of the trial. Potential disadvantages include potential for bias in comparisons between UAE and specific surgical treatments, since patients will not be randomly assigned to one type of surgery or another. Thus, while comparisons between UAE and surgery for myomata will, due to randomization, have high internal validity; comparisons between UAE and myomectomy specifically, may be more subject to bias. This bias may be controlled for during analysis if careful study is made of the factors determining the choice between myomectomy and hysterectomy.

Both to improve generalizability, and to speed enrollment, this RCT should involve multiple sites throughout the country. Data elements to be collected should encompass all those factors which panelists unanimously agreed were key to advancing knowledge in this field. Power calculations for these outcomes are shown in Table 6. Panel members agreed that data should be collected for a three to five year period following enrollment to ensure adequate information on premature menopause experienced by women enrolled in the trial.

Registry

Expert panel members felt that a registry of patients undergoing uterine artery embolization would be a valuable research element both because of its relatively low cost and because of the rapidity with which such a registry could begin yielding usable data. Typically, registries are disease based and gather data on individuals with a particular condition or exposure, without regard to the treatments they receive (e.g. state cancer registry, prenatal drug exposure registry). While, panelists felt that such a registry for uterine leiomyomata might be useful, they felt it would be difficult to create unless the

initiative was taken by an organization with a large, stable patient base, such as a managed care organization. As an alternative, the panel agreed that a treatment based registry would still be a key non-experimental method of obtaining information on the research questions described above. This registry, into which members of the Society for Cardiovascular & Interventional Radiology would enter specific data about technique and patient characteristics, could be initiated in a fairly short time period. The panel agreed that, while a disease based registry might not be feasible, data on control populations should be included in the registry. Two potential control groups discussed included women with uterine myomata who were untreated, and those with myomata who were treated with methods other than embolization.

Disease Specific Instrument Development

One recommendation of the expert panel concerned the need to develop an instrument to measure outcomes for UAE. No standard instruments have yet been adopted, although a study using such a health-related quality of life (HRQOL) instrument has been submitted for publication (Spies, J; personal communication). The panel recommended that an early goal of the proposed research would be to develop or refine such an instrument that is short, easy to administer, score and interpret for use in a variety of UAE studies.

The goal would be to develop an instrument that contained a generic core battery of HRQOL items supplemented with disease-specific questions for use in the population of women with uterine myomata. The instrument would contain clinical endpoints, symptoms, HRQOL, and satisfaction measures. A number of steps are involved in the development of a standardized instrument: 1) item selection, 2) item scaling, 3) item reduction, 4) reliability, 5) validity, and 6) responsiveness. Item generation includes development of an item pool based on items previously published as well as items generated from the expert panel and from patient focus groups. The expert panel identified, as part of their rating process, a number of outcomes that they felt essential and important to measure. These included both disease-specific outcomes (e.g., death, reoperation, vascular disruption due to embolization, menorrhagia) as well as HRQOL outcomes (e.g., mental health, sexual functioning).

In addition, it would be critical to conduct focus groups with patients themselves to determine which outcomes that ultimately matter to them. Patients in the focus groups should represent women at different stages of the disease and in different stages of treatment. A qualitative analysis of comments from focus group participants would be used to identify the range of important HRQOL concerns and would help guide the item selection process. For example, specific discussions can revolve around the item pool generated from the literature review. Types of questions asked during the group discussions can include whether or not items are relevant, comprehensive, redundant, inappropriate or understandable. Results can be used to reduce the number of items in the pool based on their importance, relevance and frequency of occurrence.

Once a comprehensive set of items has been generated, based on the literature review, expert opinion and focus group results, the instrument would need to be pretested on a small sample of women with uterine fibroids. Analyses of the pretest would be used to refine the instrument and to check it for clarity, and to identify problems in wording, comprehension, skip patterns and respondent burden. The revised instrument should then be administered to a larger sample of women with UAE for psychometric testing. For summated HRQOL scores, multitrait scaling analysis can be used to assess the internal consistency reliability of hypothesized scales and item convergence and discrimination across scales. Multitrait scaling also involves examining item frequencies, means, standard deviations and correlations among scales. Univariate analyses will identify items that are well-distributed across a range of possible values. They also identify items with high ceiling or floor effects. Item correlations can be used to identify items that are not strongly related to items intended to measure the same health outcome domain or that are too strongly correlated with items in a different health outcome domain. Exploratory factor analysis can be used to test for unhypothesized item groupings. To the extent that short-form measures of instruments are desirable, regression analyses can be used to identify the best subset of items within a given health domain.

Finally, validity tests should be conducted in order to understand the meaning of measures that are developed. Clinical validity can be assessed with known group comparisons of women at different stages of UAE. Tests of responsiveness to treatment can be conducted in samples of women before and after treatment.

Comparative Cost Analysis

Measuring Direct Costs:

In the past, acceptance of UAE would be based on safety and efficacy considerations alone. More recently, health plans and other large purchasers have begun to assess the costs and benefits of alternative treatments and base coverage decisions on the basis of these evaluations. This trend has created demand for more rigorous standards for cost measurement (Gold 1996).

The treatment of fibroids involves a range of medical and non-medical resources. The cost of treatment is measured in terms of "opportunity cost" in other words, the consumption of other goods and services that society gives up in providing care (Dranove 1996). These costs fall into two general categories: direct and indirect. Direct costs are defined as the value of all the resources consumed in providing treatment and dealing with the medical consequences of treatment indefinitely into the future (Luce, 1996). In the case of UAE, medical costs include the value of the consumables used during the procedure (angiography catheters, PVA material), physician and non-physician time, and marginal cost of equipment (wear and tear, opportunity cost if equipment is in full use currently). Indirect costs or productivity costs are defined as the value of work and leisure lost due to death or functional impairment as a result of treatment, as well as the cost of care provided to the patient by friends or family members (Luce 1996). (Though impaired ability to enjoy sexual activity or decrements in mental health can also be considered costs, we consider improvement in these areas after the procedure to be benefits, and to prevent double counting, do not include them under costs.)

Treatment also influences resource use in ways which appear to be unrelated to treatment. If a treatment reduces mortality, for example, then society will incur the costs of treating diseases which would otherwise not have occurred. In the case of UAE, these costs may be those associated with treating uterine (or perhaps ovarian) cancers. There has been wide debate over whether to consider unrelated future medical costs in cost calculations (Luce et al. 1996). Consensus is developing that these costs should be included in order to reduce inherent bias against treatments that improve quality of life without extending it (Meltzer 1997).

Payer organizations are not only interested in comparing the cost of alternative treatments performed on an individual basis (i.e. unit cost) but also in comparing overall demand. Demand for new treatments comes from several sources and all should be considered in estimating overall cost of providing treatment to a population of covered lives: (1) those who would have received an alternative treatment, (2) those diagnosed preferring to remain untreated, and (3) those who would otherwise remain undiagnosed and untreated if not for the presence of the new treatment. This third category of patients is increasingly relevant with the proliferation of consumer information and direct-to-consumer advertising. The size of this group depends on whether the diagnosis is clearly defined and the criteria by which physicians select treatment candidates.

Shortcomings of Administrative Data for Measuring Costs:

The proposed study focuses on the direct medical costs of UAE. Measuring medical costs is difficult. Readily available data on provider charges may not reflect resource cost. For example, data on charges presented by SCVIR staff suggests that charges for UAE may be more than two times that of abdominal hysterectomy, though panel members expressed skepticism at the idea that UAE was in reality twice as costly to perform.

Economic theory suggests that in non-competitive markets charges reflect provider beliefs about the prices that customers are willing to bear rather than the true cost of providing treatment (Dranove 1996). There is reason to think that the market for UAE is currently non-competitive because the number of suppliers is small relative to demand and entry costs are non-trivial. These considerations are probably less true of hysterectomy as it is so widely performed.

In some cases, depending on the quality of the hospital's accounting system, it may be possible to estimate costs from charges using reported cost-to-charge ratios (Dranove 1996). Even under the best of circumstances these measures are sensitive to hospital definitions of cost categories (i.e. fixed and variable costs) and make it difficult to distinguish costs associated with treatment from those "sunk" or fixed costs which would be incurred regardless of treatment.

Time and Motion Studies:

The proposed study uses a time and motion design to overcome problems of estimating costs with administrative data. Investigators directly monitor the treatment process and apply dollar values to each of the inputs. These values come from a variety of sources: local wage rates, acquisition costs, physician fees or wages. Because of their high cost per observation (as compared to the use of administrative data to estimate costs), time and motion studies are generally conducted at a one or two sites with few patients. Ideally, the size of this study should depend on the degree of variation in level and intensity of input use across patients and treatment sites, and would include multiple sites to improve the generalizability of the results.

Chronology of Studies

Figure 1 gives a projected chronology for the various research elements as well as additional details regarding specific steps in these studies. These investigations need not be conducted serially, but rather can begin simultaneously (or nearly so). Results from some components would be available within 6 months, while other results would take several years to be interpretable. Initial results could also be used to develop the additional funding needed to collect more data. Table 7 further outlines strengths, weaknesses, and time frames of the proposed designs, as well as additional information on studies or components of studies discussed by the panel but not detailed further in this report.

SUMMARY AND CONCLUSIONS

Uterine leiomyomata are a common cause of significant, and often disabling, symptoms among women. Symptomatic leiomyomata cost the U.S. health care system in excess of $1 billion per year in direct costs, are responsible for the loss of 5-10 million person-days per year of work or other activities, and result in more than 900,000 hospital days per year (more hospital days than result from either prostate or breast cancer). In addition, there are many women who, while not hospitalized or forced to stop work, have their activities limited, or their quality of life affected, by this condition.

Multiple treatments are available for the symptoms of uterine myomata, with the most common being hormonal manipulation and the use of non-steroidal anti-inflammatory

drugs (NSAID's). For those women whose symptoms are not relieved by this medical approach, an invasive procedure (generally hysterectomy or myomectomy) is required. An estimated 37-45,000 myomectomies, and between 177-366,000 hysterectomies are performed in the U.S. each year to treat uterine myomata. Despite the frequency with which these procedures are performed, there is little scientific data on the relative risks of myomectomy compared to hysterectomy, and no experimental comparisons of these procedures. The existing data, however, suggests that risks of the two procedures are similar. The cure rate for abnormal bleeding from leiomyomata is 100% for hysterectomy and approximately 80% for myomectomy. Over the long term, about one in ten women who has a myomectomy will later require hysterectomy to control persistent or recurrent bleeding. Given this information, a woman's choice of hysterectomy versus myomectomy is often made on the basis of the personal preference of the patient and physician.

Over the last several years, uterine artery embolization, an invasive radiologic technique for controlling bleeding from fibroids, has gained popularity. In the U.S., approximately 50 of these procedures were performed in 1996 but more than 800 in 1998, with more practitioners offering the procedure each year. For this project, we performed a literature search and systematically reviewed the 17 reports (16 published and one unpublished) with interpretable patient level data on the use UAE to treat symptomatic fibroids. These reports were all uncontrolled case series (USPTF Level III evidence) and involved a total of 728 patients (including 305 in the unpublished series).

These early studies demonstrate short term results of UAE roughly comparable to abdominal myomectomy, with approximately 90% of patients experiencing relief of symptoms (predominantly bleeding) after the procedure. Risks also appear similar to more established procedures. Specifically, one death has occurred in the 1,500 procedures performed to date, which is similar to the reported incidence of 11 deaths per 10,000 hysterectomies. The rates of both serious (i.e. potentially life threatening) and minor risks also appear similar between hysterectomy, myomectomy, and uterine artery embolization.

The current data on UAE, while promising, are inadequate to allow recommendations regarding its use outside of clinical trials at this time. The data are based on case series

without control groups, making it impossible to determine if these risks and benefits are truly similar. If, for example, only patients who were poor surgical candidates elected to have UAE, the risks of this procedure might appear falsely elevated. Conversely, if only the most experienced radiologists are currently performing the procedure, the effectiveness and safety of UAE might appear higher than they truly are. Furthermore, the risks of UAE in different hands might be considerably higher, particularly if large numbers of physicians begin doing few procedures (as contrasted with the few practitioners performing higher volumes as is currently the case).

Reports of UAE in the lay press have generated considerable enthusiasm, suggesting that demand for a non-surgical (albeit still invasive) treatment of myomata would be high (Gilbert,1999). The prevalence of symptomatic fibroids, the apparent high demand for a new treatment, and the rough equivalence of outcomes among UAE, hysterectomy, and myomectomy suggest that controlled trials of these treatments would be feasible, ethical, and desirable. The expert panel concluded that beginning a properly designed randomized, controlled trial would be crucial in establishing the comparative risks and benefits of UAE, hysterectomy, and myomectomy. The panel further believed that the validity of such a trial would be enhanced by careful measurement of several short and long term outcomes. Key short term outcomes which the panel agreed should be included were: death, reoperation (e.g. hysterectomy for infection following UAE), and operative injury. Long term outcomes similarly identified included: menorrhagia, premature menopause, recurrence of myomata requiring hysterectomy or myomectomy, mental health, pain during sexual activity, satisfaction with treatment, technical failure rate of the procedure, frequency of use of medical therapy after the procedure (e.g. hormonal therapy to control bleeding), and quality of life (as measured by a disease-specific quality-of-life instrument).

The type of quality-of-life measure identified by the panel does not now exist for this group of patients, and general quality-of-life measures (such as the SF-36) tend to be less appropriate for a relatively young and healthy group of individuals, like the women who suffer from uterine myomata. For these reasons, the panel felt that the development of such a measure should be a key focus of research into uterine artery embolization, and that once developed, this measure could be incorporated into both experimental and non-experimental studies of UAE.

Given the current healthcare environment, in which cost considerations are often primary when evaluating new treatments, the expert panelists agreed that careful study of the costs of UAE should also be a priority. There are multiple ways of measuring cost, each with its advantages and disadvantages. The panel agreed that a time and motion study would provide important information about the actual resource use of embolization, as distinct from charges for the procedure, which can vary tremendously from practitioner to practitioner. Further information about cost could also be obtained as part of a randomized trial, if cost measures are included as part of the data collection design.

Finally, the panel believed that establishing a registry of patients undergoing uterine artery embolization could provide non-experimental data on the risks and benefits of UAE, as well as provide data on patient selection, technique, and diffusion of the procedure throughout the country. Such a registry would collect answers to a standard panel of questions about the radiologist performing the procedure, technique, patient demographics, symptoms, and long and short term outcomes (including complications). The utility of a registry could be increased by soliciting data on a comparison group, either women with uterine myomata who do not undergo UAE (i.e., have either standard interventions, or no intervention), or with an "unselected" population of women in similar demographic strata. This type of registry would be relatively less costly to implement than a randomized trial, and would provide information more rapidly than an RCT, albeit with less reliability and validity due to the use of non-experimental methods. Registry data would be useful in specifying specific questions to be answered by an RCT but would not be a substitute for such a controlled trial.

Symptomatic uterine leiomyomata are a significant source of distress to many women, and place a substantial burden on our health care system. New techniques that promise to provide relief from this suffering deserve careful consideration. Traditionally, surgical procedures have been poorly studied until after they have been widely used. The approach taken in reviewing uterine artery embolization involved a careful review of the literature by experts who then described the elements of a broad research agenda for investigating this technique. If the process we described can guide the acquisition of knowledge in this field it may serve as a model for evaluating other new technologies before they become widely adopted.

TABLE 1: ANNUAL VOLUME: PROCEDURES TO TREAT UTERINE LEIOMYOMATA, 1990-1998

	Hysterectomy total	Hysterectomy for fibroids (lower bound)*	Hysterectomy for fibroids (upper bound)*	Myomectomy	Uterine Artery Embolization
1990	586,000	175,800	363,320	38,000	0
1991	540,000	162,000	334,800	46,000	0
1992	574,000	172,200	355,880	45,000	0
1993	546,000	163,800	338,520	44,000	0
1994	556,000	166,800	344,720	39,000	0
1995	583,000	174,900	361,460	38,000	0
1996	591,000	177,300	366,420	37,000	50
1997					200
1998					800

Data on UAE from Boston Scientific, personal communication, 1999
Data on hysterectomy and myomectomy from National Hospital Discharge Surveys 1990-1996
* Upper and lower bounds calculated from estimates of proportion of hysterectomies performed to treat uterine fibroids

TABLE 2: PROCEDURES PERFORMED TO TREAT UTERINE LEIOMYOMATA, BY PATIENT AGE

	Hysterectomy	Myomectomy	UAE
Age	n (%)	n (%)	n (%)
15-44	327000 (59)	32000 (86)	320 (40)
45-64	203000 (32)	5000 (13)	480 (60)
>64	5000 (9)	<1%	0 (0)
Total	581000	38000	800

Numbers rounded to nearest 1000, except UAE
Hysterectomy and myomectomy data based on National Hospital Discharge Survey 1996
UAE data based on personal communication, Boston Scientific, 1999

TABLE 3: EVIDENCE TABLE COMPARATIVE OUTCOMES OF TREATMENTS FOR UTERINE LEIOMYOMATA

	Hysterectomy	Myomectomy	Uterine Artery Embolization	Comment
SHORT TERM OUTCOMES (<45 days after procedure)				
Death (per 10,000 procedures)	11[a] (4-36)	†	†	
Transfusion (% of patients receiving at least 1 unit)	(2 – 13)[a]	(20 – 32)[b,c]	<1	LaMorte and Iverson: Includes "elective" transfusion of autologous blood; Walker: Transfusion reported 4 weeks after embolization.
Reoperation (embolization, myomectomy, hysterectomy)	(0.2-1)[a]	1[c]	5	UAE: Some operations may have occurred after >45 days, but reports are ambiguous
Operative injury (% of patients experiencing injury to bowel, bladder, or ureter)	<1[a]	<1[c]	0	
Thromboembolic events (% of patients experiencing deep venous thrombosis or pulmonary embolism)	<1[a]	†	<1	
Febrile morbidity (% of patients)	15[a]	13 (10-25)[c]	8;25	8% figure represents exclusion of a single large unpublished study and a report which may represent duplication of patients from another study,25% includes these studies.
Urinary tract Infection (% of patients)	(3-10)[a]	3[b]	†	
Operative site infection (% of patients)	7[a]	<1[b]	2	2/88 patients with infection after UAE
Wound infection (% of patients)	(2-10)[a]	<1[b]	<1	
Femoral nerve injury (% of patients)	<1[a]	†	N/A	
Vascular disruption to limb or internal organs due to embolization (% of patients)	N/A	N/A	0	Walker: reported 1 patient with embolization material in ovarian artery.
Pain (# days after procedure until pain resolved)	14 (1-140)[e]	†	(1-60)	
LONG TERM OUTCOMES (>44 days after procedure)				
Physical Health				
Death	Possible affect, direction and magnitude unclear	†	†	

Estimates presented as a point estimate and range (in parenthesis), with the point estimate representing a weighted average of the various studies.
If study measures were heterogeneous, estimates are given as range (in parenthesis) only.
Data on UAE are derived from literature listed in UAE Literature Summary Table.
† No data or data inadequate to present meaningful estimates.

TABLE 3: EVIDENCE TABLE COMPARATIVE OUTCOMES OF TREATMENTS FOR UTERINE LEIOMYOMATA (CONTINUED)

	Hysterectomy	Myomectomy	Uterine Artery Embolization	Comment
Menorrhagia (% of patients improved)	100	81 (40-93)[d]	90	
Anemia (% of patients improved)	100[e]	†	†	Carlson: 43/418 women had anemia pre-hysterectomy, all were improved after surgery.
Pelvic pain (% of patients with indicated change)	Improved: 92[f]-95[e] Worsened: 1[f] New Onset: 2-3[e]	†	Improved: 87 (n=16)	Carlson: 259/273 patients with pain before surgery had improvement in pain after hysterectomy. 1/33 patients without pain before surgery developed pain after hysterectomy. Schofield: 98/106 patients with pain before surgery had improvement in pain after hysterectomy. 3/69 patients without pain before surgery developed pain after hysterectomy.
Uterine size reduction (% of patients with reduction in size)	100%	100%	98 (n=35)	
Urinary problems (% of patients with indicated change in incontinence and frequency)	Improved: 60-91[e,f] New Onset: 4-8[e]	†	Improved: 94(n=35)	Carlson: 125/137 patients with urinary problems before surgery were improved after surgery. 11/141 patients without urinary problems pre-op developed them after surgery.
Mass related symptoms (% of patients with improvement in bloating, abdominal swelling)	See comment	†	89	Carlson: overall improvement in mass symptoms, specific data not given.
Fatigue (% of patients with indicated change)	Improved: 80[e] New Onset: 0	†	†	
General Health Index from SF-36 (% improvement in score)	49[e]	†	†	Carlson: absolute increase from 53 pre to 79 post procedure
Premature menopause (excluding hysterectomy with oophorectomy)	Possible effect, magnitude unclear[a]	†	5	Premature menopause may result in Coronary Artery Disease and osteoporosis, although the magnitude of this risk is unclear.
Vaginal vault prolapse	Insufficient data to estimate[a]	†	N/A	

TABLE 3: EVIDENCE TABLE COMPARATIVE OUTCOMES OF TREATMENTS FOR UTERINE LEIOMYOMATA (CONTINUED)

	Hysterectomy	Myomectomy	Uterine Artery Embolization	Comment
Adverse reaction to embolic agent	N/A	N/A	0	
Cervical and uterine cancer	N/A	†	†	Long term risk of uterine and cervical cancer is essentially zero if entire uterus removed.
Recurrence of Uterine Fibroids				
Recurrence not requiring surgical treatment (%)	0	15 (4-30)[d]	†	Data on asymptomatic myomata vs. symptomatic myomata not requiring surgery cannot be separated based on published literature. Data on UAE limited to 1-2 years of follow-up
Recurrence requiring hysterectomy or myomectomy (%)	0	10 (3-32)[d]	<1	
Mental Health				
Mental Health Index from SF-36 (% improvement in score)	23[e]	†	†	Carlson: absolute increase from 61 pre to 75 post procedure
Depression (% of patients reporting indicated change)	Improved: 35[e] Worsened: 8[e]	†	†	
Anxiety (% of patients reporting indicated change)	Improved: 32[e]-50 Worsened: 6[f]	†	†	
Social/Role Function				
Social Activity Index from SF-36 (% increase in index score)	56[e]	†	†	Carlson: absolute increase from 52 pre to 81 post procedure
Days to normal activity (days)	42 (0-119)[e]	†	†	Carlson: measured only in those working outside the home
Sexual Function				
Interest in sexual activity (% of patients with indicated changes)	Improved: 26[e]-56[f] Worsened: 5[f]-9[e]	†	†	
Enjoyment of sexual activity (% of patients reporting indicated change)	Improved: 40[e]- 50[g] Worsened: 12[e]-20[g]	†	†	
Frequency of sexual activity	Increased[f]	†	†	Schofield: specific data not given
Pain during sexual activity (% reporting indicated change)	Improved: 85[f] Worsened: 0[e]-2[f] New Onset: 7[f]	†	†	Schofield: 34/40 patients with pain before surgery improved after surgery, 1/40 worsened, and 13/175 had new onset pain.

TABLE 3: EVIDENCE TABLE COMPARATIVE OUTCOMES OF TREATMENTS FOR UTERINE LEIOMYOMATA (CONTINUED)

	Hysterectomy	Myomectomy	Uterine Artery Embolization	Comment
Satisfaction				
(% satisfied with procedure)	96[f]	†	85; 90	Schofield: would make same decision (to have hysterectomy) again
Cost*				
Charges ($) Hospital Physician	 5,400 2,300	 4,900 2,100	 9,300 4,000	Estimates of costs and charges based on data from 1) procedure specific literature, 2) Medicare Payment Advisory Committee, and 3) Bureau of Labor Statistics. Hysterectomy data based on weighted averages of abdominal, vaginal, and laparoscopically assisted hysterectomies.
Indirect Cost (Lost workdays/$)	5,600	4,800	500[i]	
Utilization of Services				
Length of Hospital Stay (days)	Abdominal: 4.2[h] Vaginal: 2.8[h]	3.3[h]	(1-1.5)	
Number of follow-up visits until full recovery	†	†	†	

[a]Bernstein, 1997
[b]LaMorte, 1993
[c]Iverson, 1996
[d]Buttram, 1981
[e]Carlson, 1994
[f]Schofield, 1991
[g]Heldstrom, 1993
[h]Graves, 1996
[i]Boston Scientific, Personal Communication, 1999

TABLE 4: LITERATURE SUMMARY
UTERINE ARTERY EMBOLIZATION LITERATURE SUMMARY TABLE

Author	Year	Design	Peer Reviewed	Sample Size	Age (median or range)	Technical Success Rate	Menorrhagia resolved or improved	Time to Symptom Assessment (Months)	Patient Satisfaction (% satisfied)	Complications (requiring re-hospitalization or reoperation)
Journal Articles										
Ravina	1995	Case series	Yes	16	44.1	87% (14/16)	64% (9/14)	11-48	No data	12% (2/16)
Ravina	1997	Case series	Unknown	88	34-51	94% (83/88)	90% (60/67)	2-6	No data	8% (7/88)
Goodwin	1997	Case series	Yes	11	44.2	100% (11/11)	86% (6/7)	2-9	87% (7/8)	9% (1/11)
Bradley	1998	Case series	Yes	8	37.5	No data	80% (4/5)	3-9	71% (5/7)	25% (2/8)
Ravina	1998	Case series	Yes	81	44	95% (77/81)	89% (68/76)	12	No data	6% (5/81)
Worthington-Kirsch	1998	Case series	Yes	53	43	98% (52/53)	96% (50/52)	3	94% (49/52)	4% (2/53)
Hutchins	1999 (unpublished)	Case series	Unknown	305	26-52	96% (292/305)	87% (155/179)	12	84%	4% (13/305)
Abstracts										
Vedantham	1997	Case series	Yes	10	44.2	100% (10/10)	86% (6/7)	2	No data	No data
Stancata-Pasik	1998	Case series	Yes	12	No data	No data	100% (8/8)	2	No data	No data
Goodwin	1998	Case series	Yes	25	No data	No data	No data	No data	No data	16% (4/25)
Katz	1998	Randomized trial*	Yes	10	No data	No data	100% (10/10)	2	No data	None
Ravina	1998	Case series	Unknown	184	43 mean	No data	91%	30	No data	No data
Walker	1998	Case series	Unknown	88	No data	No data	No data	12	>80%	3% (3/88)
Le Dref	1998	Case series	Yes	81	44 mean	No data	No data	No data	No data	No data
Spies	1998	Case series	Yes	26	No data	100% (26/26)	88% (15/17)	3	94% (16/17)	8% (2/26)
Pron	1999	Case series	Yes	24	38-52	100% (24/24)	No data	No data	No data	0% (0/24)
Spies	1999	Case series	Yes	49	No data	98% (48/49)	89% (24/27)	3	88%	6% (3/49)

* Randomized to one type of embolic agent vs. another

TABLE 5: FINAL PANEL RATINGS: KEY OUTCOME MEASURES FOR STUDIES OF UAE

	Should not be measured	Useful to measure	Important to measure	Essential to measure
SHORT TERM OUTCOMES				
(<45 days after procedure)				
Death				10
Transfusion		1	3	6
Reoperation			1	9
Operative injury			2	8
Thromboembolic events		1	4	5
Febrile morbidity		5	3	2
Urinary tract Infection	1	7	1	1
Operative site infection		1	2	6
Wound infection		2	4	3
Femoral nerve injury	1	1	2	6
Vascular disruption to limb or internal organs due to embolization	1	1	2	6
Pain		3	4	3
LONG TERM OUTCOMES				
(>44 days after procedure)				
Physical Health				
Death		1	1	8
Menorrhagia				10
Anemia		1	6	3
Pelvic pain		1		9
Uterine size reduction		3	3	4
Urinary problems		3	4	3
Mass related symptoms		1	4	5
Fatigue	5	2	2	
General Health Index from SF-36		3	3	4
Premature menopause			2	8
Vaginal vault prolapse	2	1	3	3
Adverse reaction to embolic agent	1		1	8
Cervical and uterine cancer	2	3	3	2
Recurrence of uterine fibroids				
Recurrence not requiring surgical treatment	2		2	6
Recurrence requiring hysterectomy or myomectomy			1	9
Mental Health				
Mental Health Index from SF-36			4	6
Depression		2	3	4
Anxiety		2	2	5

TABLE 5: FINAL PANEL RATINGS: KEY OUTCOME MEASURES FOR STUDIES OF UAE (CONTINUED)

	Should not be measured	Useful to measure	Important to measure	Essential to measure
Social/Role Function				
Social Activity Index from SF-36		2	3	5
Time to return to normal activity		1	2	7
Sexual Function				
Interest in sexual activity		1	5	4
Enjoyment of sexual activity		1	3	6
Frequency of sexual activity		1	3	6
Pain during sexual activity			1	9
Satisfaction				
Satisfaction with treatment			1	9
Cost				
Direct Cost		1	2	7
Indirect Cost		1	2	7
Utilization of services				
Length of Hospital Stay		1	2	7
Number of follow-up visits until full recovery		1	3	6
Other				
Technical failure rate			2	8
Use of medical therapy after procedure			4	6
Pregnancy rate		1	5	4
Spontaneous abortion rate		2	4	4
Pregnancy complications		2	2	5
Ovarian function (FSH level)		1	4	5
Characteristics of women choosing UAE		1	3	5
Radiation exposure		4	2	4
Patient understanding of risks and benefits of procedure		1	5	4
QOL as rated by disease specific measure			3	5

TABLE 6: POWER CALCULATIONS FOR RANDOMIZED TRIAL[a]

Outcome	Observed Levels[b]	Required Sample Size (Each Group) to Detect a Difference Between Surgical (myomectomy and hysterectomy) and UAE[c]
Death	Hysterectomy = .01% UAE = .01%	c
Reoperation	Hysterectomy = 0.5% Myomectomy = 1% UAE = 5%	287
Operative Injury	Hysterectomy = 1% Myomectomy = 1% UAE = 0%	970
Menorrhagia (% improved)	Hysterectomy = 100% Myomectomy = 81% UAE = 90%	3313
Premature Menopause	Hysterectomy =1% UAE=5%	333
Recurrence requiring hysterectomy or myomectomy	Hysterectomy = 0% Myomectomy = 10% UAE = 20%	219
Mental Health	0.25 SD difference between hysterectomy/ myomectomy and UAE	503
Pain during sexual activity	Hysterectomy = 85% Myomectomy = 40% UAE = 40%	82
Satisfaction with treatment	Hysterectomy = 90% Myomectomy = 87% UAE = 87%	4243
Frequency of use of medical therapy after procedure	Hysterectomy = 0% Myomectomy = 15% UAE = 15%	304

[a] 2-sided test with alpha = 0.05. Number in each group needed to achieve 80% power, assuming 50% of surgical group is hysterectomy and 50% is myomectomy.

[b] Based on literature or expert opinion

[c] Due to similarity of observed death rates and the rarity of the outcome, a study with 10,000 patients per arm would have 0.23 power to detect a five-fold increase in death from UAE vs. hysterectomy.

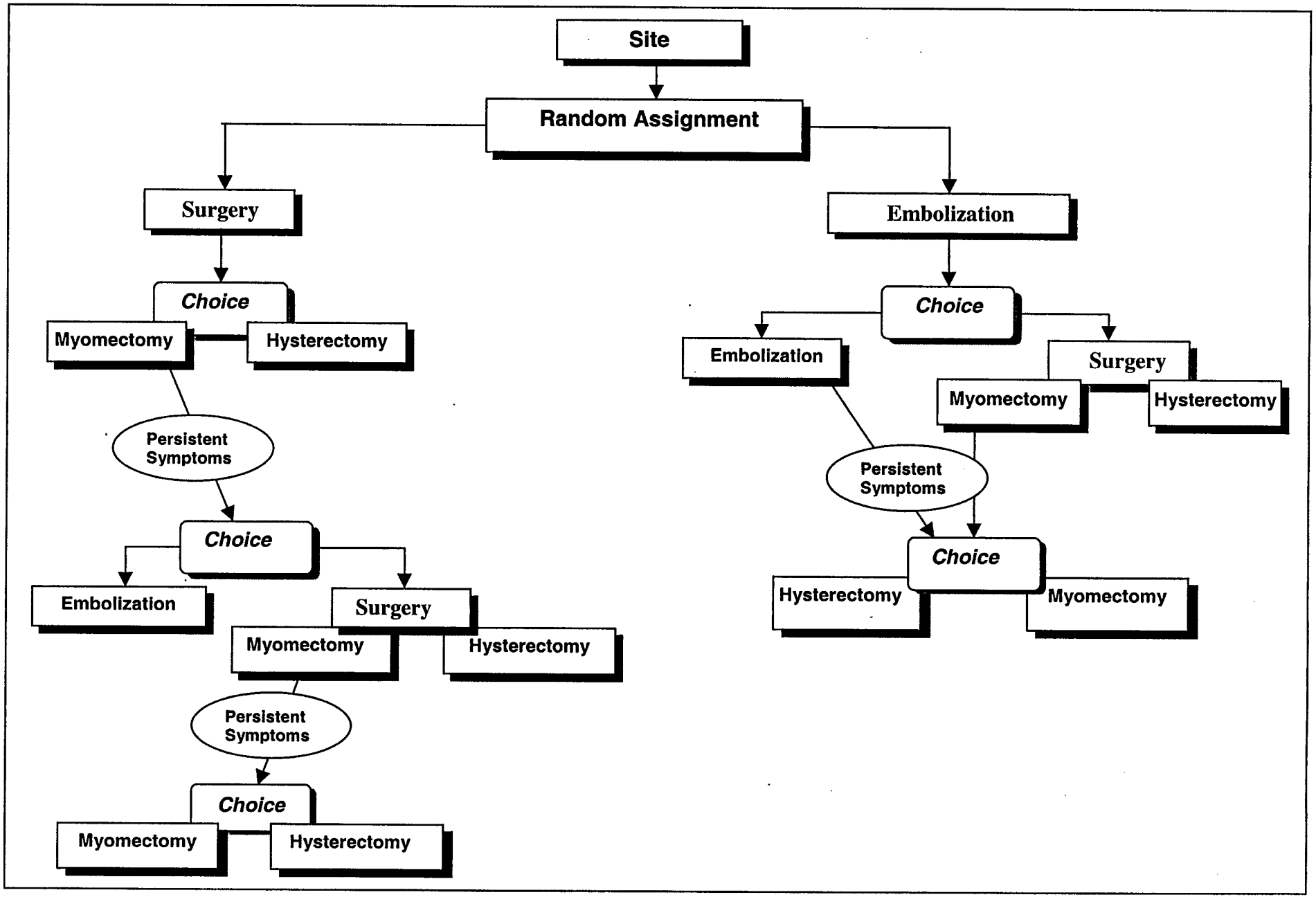
TABLE 7: STUDY DESIGNS AND RESEARCH DOMAINS

Study Design	Time Frame	Outcomes	Strengths	Weakness	Notes
Hybrid: RCT:UAE vs. Surgical treatments Cohort trial on surgical arm where patient and physician choose hysterectomy vs. myomectomy	5-7yrs	Early Relief of symptoms Satisfaction with treatment QOL, sexual function, activity Costs (not charges, including indirect costs, and all direct medical costs) 3year relief of symptoms recurrence satisfaction menopause (FSH) 5year menopause (FSH) QOL Relief of symptoms	Overcomes objections to being assigned to hysterectomy arm.	The comparisons can be very complex with hybrid design Potential for selection effects weakens inferences.	Needs treatment selection component (hysterectomy vs. myomectomy) to control for selection.
Prospective Registry of UAE vs. General Population	Indefinitely into the future	QoL Symptoms (pain, bleeding, pressure, infertility) Pregnancy rates (Abortion rate, pregnancy complications [IUGR]) Long term complications (premature menopause [increased FSH]) Recurrence (requiring medical treatment, requiring surgery)	Allows good baseline data Standardized measures across UAE patients Offers relevant comparisons on broad QoL questions	Doesn't offer comparative information upon which to base treatment and coverage decisions.	If such a registry already existed, it would be inexpensive to do such comparisons.
Prospective Registry of Women with Symptomatic Myomata	Indefinitely into the future	Same as above	Offers the potential for meaningful comparisons of relevant treatments. Because care is *not* delivered under protocol, it may be feasible to obtain information about cost and outcomes in clinical practice. Stronger external validity compared to RCT.	Lack of randomization means selection effects may bias results.	This type of study needs to include a treatment choice component to control for patient selection statistically. Data collected here may be important in analyzing and interpreting RCT results.
Focus group on acceptability of RCT	3 months	Patient and MD acceptance of RCT model in this setting	Would need to be done to get RCT funding Could be used to design QOL instrument		
Design disease specific QOL measure	6 months	Would identify relevant outcome domains for this group of patients	Would improve ability of other trials to detect meaningful differences		Focus group would be part of this approach
Cost Study UAE vs. Hysterectomy This study could be prospective or retrospective or mixed.	10 months	Direct costs of treatment materials labor room and board Indirect costs Impact on work and leisure activities.	Very important data to collect especially in the context of a managed care dominated payment system. Data *not* collected as part of RCT should have good external validity. Rapid results overcome limitations of using administrative data	Depends on design May be difficult to compare to costs of other treatments	The only information on costs to date is on charges. However, charges are not a good measure of costs, particularly in the case of the physician component. Costs for materials are easier to obtain. It is likely that some cost analysis will have to be done even if an RCT proceeds.

Figure 1: Research Agenda – Study Chronologies

	YEAR 1	YEAR 2	YEAR 3	YEAR 4	YEAR 5	YEAR 6	YEAR 7
Randomized Trial	• Pre-proposal Study Design • Proposal Development/Funding • Site recruitment/IRB • Sample design/evaluation design/instrument development • Patient selection/recruitment • Patient enrollment consents • Baseline patient survey	• 1 year patient Survey • Analysis		• Obtain 3 Year Documentation • 3 year patient survey • 3 year analysis		• Obtain 5 Year Documentation • 5 Year Patient Survey • Obtain Administrative Data • Analysis Final Report	
Registry	• Solicit comments from interventional radiologists • Design form • Initiate awareness campaign • Begin data collection	• Continued data collection ---------- • Periodic data analysis ----------					
QOL Instrument Development	• Collate items and available literature • Conduct focus group • Draft questionnaire • Pilot questionnaire • Analyze data • Do larger validation study • Analyze data • Draft final questionnaire						
Time – Motion Study	• Finalize research design • Select sites and participating physicians • Obtain secondary data on local wage rates, cost of materials, and other inputs • Collect time and motion data • Build analytic data files • Analyze data						

Figure 2: Randomized Control Trial Study Design



Appendix A

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